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Primary neuroprotection

The Holy Grail of multiple sclerosis therapy



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There are 7 FDA-approved therapies for relapsing forms of multiple sclerosis (MS), and over a dozen more in various stages of development. Some of these therapies are highly effective, reducing new gadolinium-enhancing lesions on brain MRI by 90% or more compared to placebo. Along with reduced active inflammation, a concomitant slowing in progressive disability and brain atrophy has been reported with most approved therapies and many currently in development. But the slowing of disability accrual and atrophy should not be surprising with these therapies: prevention of acute injury leads to preservation of tissue, i.e., secondary neuroprotection.

This bright hope for overtly inflammatory forms of MS contrasts with ongoing challenges in purely progressive forms of MS, which include primary progressive MS (PPMS) and secondary progressive MS (SPMS) without relapses. Many therapies with efficacy in relapsing MS, including interferon- β , glatiramer acetate, mitoxantrone, and rituximab, have produced disappointing results in clinical trials of purely progressive MS. Primary neuroprotection has proven to be a harder nut to crack than antiinflammation. Robust therapies to slow neurodegeneration are likewise lacking in Alzheimer, Parkinson, and other neurodegenerative diseases.

One of the challenges in developing neuroprotective therapies for progressive MS is a twofold predicament: What biologic pathway should be targeted, and what imaging metric should be used to test therapies that perturb these pathways? Without a pathway to target, we are unable to define a useful metric for clinical trials; without a defined metric, we are unable to test a therapy that modifies a potentially important pathway.

In this issue of *Neurology*®, Barkhof et al.¹ report the results of a 12-month, placebo-controlled, phase II trial of the phosphodiesterase inhibitor ibudilast in 297 patients with relapsing forms of MS (relapsing-remitting MS [RRMS] and SPMS with superimposed relapses). They also report an additional 12

months of open-label follow-up, totaling 24 months of therapy for some patients. The original goal was to evaluate the antiinflammatory effects of ibudilast, but little difference between treatment groups was seen in either active lesions or clinical relapses. Despite no apparent effect on overt inflammation, a preplanned evaluation of brain atrophy found a dose-dependent decrease in atrophy progression in ibudilast-treated patients compared to placebo. In addition, a preplanned evaluation of progressive disability found less disability progression among those on active treatment for the entire 2 years vs those initially on placebo, although no difference was seen at 1 year.

Might ibudilast be neuroprotective, with no effect on overt inflammation? This possibility was further explored with a post hoc analysis evaluating the proportion of gadolinium-enhancing lesions converting to T1 hypointense lesions, also called T1 holes. T1 holes represent areas of severe axon loss, which is the final common endpoint thought to underlie irreversible brain atrophy and clinical disability in MS.² The prevention of active inflammatory lesions later converting into T1 holes is therefore one proposed measure of neuroprotection.³ Supporting their brain atrophy and disability observations, Barkhof and colleagues found that ibudilast-treated patients had a dose-dependent reduction in the proportion of gadolinium-enhancing lesions converting to T1 holes at 24 months.

This study provides Class III evidence for the possible neuroprotective effect of ibudilast in MS. While further confirmation will require larger trials which use progressive clinical disability as the primary outcome, it is interesting to speculate on how phosphodiesterase inhibitors might have neuroprotective properties. Inflammation is typically considered infiltration of peripheral blood immune cells, but the activated resident microglia and meningeal B-cell follicles found in progressive MS may represent a simmering inflammatory state which is independent of

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peripheral inflammatory infiltrates. Activated microglia can release tumor necrosis factor- α and other cellular mediators that can damage both neurons and oligodendrocytes and, in turn, may lead to neurodegeneration and atrophy. Microglial activation is hypothesized to play a role in several degenerative processes such as Alzheimer disease and Parkinson disease,^{4,5} and, importantly for ibudilast, can be modulated by phosphodiesterase inhibitors.^{6,7} Perhaps primary neuroprotection in progressive MS may have a component of antiinflammation after all. The smoldering form of inflammation manifest by microglial activation appears to be present in relapsing forms of MS, too, so may join together with the peripherally infiltrating inflammation to contribute to ongoing tissue damage throughout the early stages of disease. Other potential noninflammatory mechanisms by which phosphodiesterase inhibitors may exert a protective effect on the brain include inhibition of leukotrienes and nitric oxide synthesis and protection against astrocyte apoptosis. Altogether, it appears that the innate immune system may be interwoven into CNS homeostasis in a way that blurs the conceptual distinction between neuroprotection and antiinflammation.

Turning finally to the imaging metric portion of our neuroprotection predicament, T1-hole conversion is only useful in MS with active lesion formation, and enhancing lesions are relatively rare in purely progressive MS. Other imaging modalities are needed to measure neuroprotection in PPMS and SPMS. Candidate metrics for use in the absence of active inflammatory lesions include magnetization transfer imaging, diffusion tensor imaging, optical coherence tomography, and proton magnetic resonance spectroscopy. All of these have shown reasonable reliability and reproducibility in multicenter studies, and each has its own strengths and drawbacks as a measure of neuroprotection. None of these methods are specific to microglial activation or any other molecular pathway, but they all measure tissue integrity and could be useful metrics of neuroprotection.

There are many potential biologic pathways to target for neuroprotection in MS, and several candidate imaging metrics are also available. Although the lines between primary and secondary neuroprotection are becoming less clear, it appears that we are getting closer to finding the Holy Grail of neuroprotection in MS.

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